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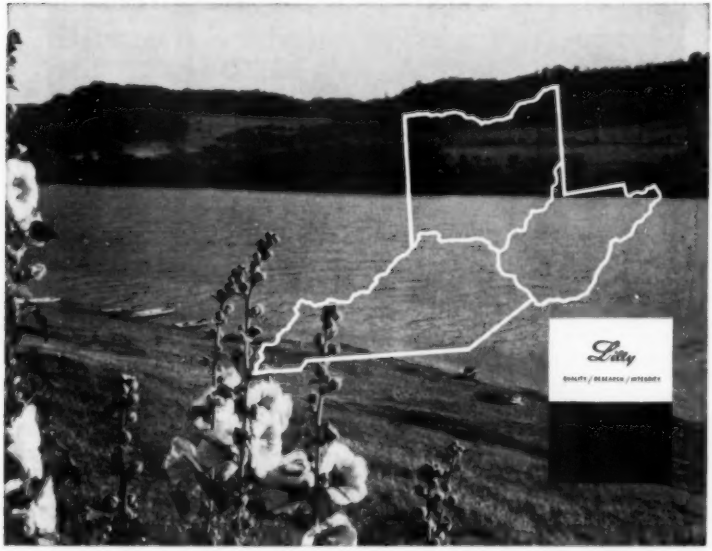

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EDITORIAL

SELF-SERVICE OF DRUGS AND MEDICINES

A NUMBER of state pharmaceutical associations have adopted similar resolutions on a key problem. Such action is both commendable and long overdue. In direct and positive language, they condemn the sale of drugs and medicines by self-service, even in pharmacies, and suggest that all drugs including the usual home remedies be sold either by the pharmacist or under his direct and immediate supervision.

The circumstances leading to such action by organized pharmacy are both varied and complex. First, no one can deny that since the passage of the Durham-Humphrey Amendment the manufacturers of over-the-counter proprietary drugs have engaged in a vigorous campaign to greatly widen the number and type of retail outlets for their now FDA "sanctioned" products. This effort was greatly intensified by the mass selling of drugs made possible by consumer advertising on television. The fact that the Durham-Humphrey Amendment gives permission, and in fact insists, that drugs labeled with adequate directions for use be sold over the counter without specifying the type outlet was seized upon as an endorsement of any type of retail establishment. Those states having pharmacy acts or dangerous drugs acts restricting such promiscuous distribution were claimed to be operating under obsolete standards. "Why," asked certain of these manufacturers, "should a state have more stringent rules than the Federal Government?" These state laws have been challenged in the courts and one of the key arguments has been the use of self-service by pharmacists themselves. This, so the argument went, justifies the sale of these drugs in the supermarket or anywhere else by anyone. The error in logic of justifying an evil by citing a similar and equal evil, while it seems apparent and obvious, was not so considered by some called upon to decide the issue. Some few physicians are known to let their office nurse or wife, in their absence, dispense drugs to patients but should this be used to alter or abolish medical practice acts?

As far as the self-service of drugs is concerned, this of course is wrong, it has always been so, and it will continue to be, laws or no laws. The growth of this practice in retail pharmacy has been largely a matter of economic self-defense. Like all acts of expediency, however, the consequences have proven worse than the situation which pharmacists were trying to avoid. Anyone well informed today knows that unscientific, careless self-medication is growing to alarming proportions. The profit-conscious and conscienceless manufacturers of many of these drugs using television and radio advertising costing millions have convinced the public that drugs are just as essential in one's daily life as air, water, and food; thus, mottoes like "take an aspirin break!" The drugs which they purvey, however, are not simple remedies but drugs having potent action on the central nervous system, both stimulants and depressants; anticholinergic agents; sympathomimetics; and antibiotics—and the list still grows.

Quite contrary to what our opponents claim, pharmacists *are* concerned with something more than the economics involved in the distribution of drugs. Their training and knowledge as well as their daily contacts give them a full realization of just what is happening to the public at large. They also know that labeling with adequate directions for use is a farce. Even if it were true, few laymen could interpret it and still fewer even try. Their knowledge of the drug is what the modern medicine man on TV shouts at them and what the Federal Trade Commission permits here is often shameful. Self-service accompanied by this blatant advertising approach almost completely eliminates any concern or caution about any drug product. This is why pharmacists whose professional duty it is to safeguard public health must abandon self-service of drugs and institute tightened measures to give the public a more safe and sane attitude when these medicines are purchased and used.

L. F. Tice

DIHYDROCODEINE

A Pharmacologic Review

By Benjamin Weiss *

ALTHOUGH dihydrocodeine cannot be considered a new molecule, having been prepared in Germany by Skita and Franck in 1911 (1), and although its effectiveness as an antitussive was reported by Fraenkel (2) as early as 1913 for which purpose it has been widely employed in Europe and Japan, relatively little attention was accorded this drug with respect to its analgesic activity until recently.

Some of the earlier work performed with this compound merits citation. In 1916, Macht (3) found that dihydrocodeine increased the tonus and activity of *in situ* rabbit ureteral preparations. Macht and Fisher (4) determined the toxicity of opium alkaloids on *Paramecium putrinum*. They reported that the morphine group of alkaloids was non-toxic or very slightly toxic; whereas, the papaverine group was very toxic to the organism examined. It is interesting to note that this represents one of the first biological separations of the phenanthrene and isoquinoline groups of opium alkaloids.

Ahlgren (5), in 1930, demonstrated a difference between the morphine-like alkaloids and the dihydrogenated derivatives (dihydrocodeine) in regard to their ability to replace insulin in a series of tissue oxidation reactions. Morphine and codeine possessed a mild insulin-like action, but dihydrocodeine and other dihydrogenated derivatives did not manifest this property. More recently, Schmitz (6) studied the effect of these alkaloids on the oxygen-uptake of mouse ascites tumor cells and found that, while morphine did not have an inhibitory effect in concentrations up to 500 mcg./ml., codeine and dihydrocodeine were inhibitory in threshold concentrations of 35-70 mcg./ml. and 70-100 mcg./ml., respectively. He concluded that there was no relation between the effect of these alkaloids on cellular metabolism and their activity as mitotic poisons. While these studies are of interest, this report is concerned primarily with

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those actions of dihydrocodeine which are regarded as being more characteristic of narcotic analgesics.

Comparative Analgesic Activity. In 1926, Heinroth (7) investigated the analgesic activity of dihydrocodeine in humans. He found that 20 mg. of dihydrocodeine given orally reduced the sensitivity of the teeth to faradic stimulation less than 10 mg. of morphine but more than 50 mg. of codeine. In the doses used, dihydrocodeine appeared to have no adverse effects. Clinicians apparently failed to appreciate the significance of this observation for it was not until very recently that any concentrated clinical evaluation of the analgesic activity of dihydrocodeine was undertaken. Gravenstein *et al.* (8), in 1956, reported on the value of dihydrocodeine in postoperative pain. Prior to subcutaneous administration of medication, each subject was required to rate the pain as "bearable" (moderate pain) or "severe". Patients reporting slight pain, or pain occurring only on motion, did not qualify for the study. Drugs were administered and evaluations of responses were made on the basis of the "double blind" approach. These investigators found that 30 mg. of dihydrocodeine approached the potency of 10 mg. of morphine. This observation was of particular interest in view of the "absence" of side-effects following the 30 mg. dose of dihydrocodeine. Reduction of the dose of dihydrocodeine to 15 mg. resulted in marked decrease of analgesic potency; whereas, an increase to 45 mg. did not improve the response. The authors point out that although 10 mg. of morphine provided slightly greater relief of pain than 30 mg. of dihydrocodeine, the superiority of the former was not statistically significant unless a rigid criterion (i.e., complete relief) was applied. Using this criterion, morphine was shown to be consistently more effective than dihydrocodeine. Beecher *et al.* (9) extended their evaluation, comparing 60 mg. of dihydrocodeine with 10 mg. of morphine, each given alternately to the same postoperative patients by subcutaneous injection. The relief afforded by this dose of dihydrocodeine was almost but not quite equal to that of the standard (10 mg.) dose of morphine.

Stimulated by these reports of an analgesic with a potency approximating that of morphine but with minimal untoward reactions, several other investigators studied the analgesic activity of dihydrocodeine in a number of clinical situations.

Keats, Telford, and Kurosu (10) repeated the studies of Gravenstein *et al.* (8) using 30, 60, and 90 mg./70 Kg. of body weight compared to 10 mg./70 Kg. of morphine in postoperative patients. Dihydrocodeine in a dose of 30 mg. was 9% less effective than morphine; 60 mg. was as effective as morphine, but 90 mg. produced no greater analgesia than 60 mg. In a subsequent report (11), these investigators noted a slight decrease in analgesia at 90 mg. compared to 60 mg. of dihydrocodeine. This was also observed with other potent analgesics studied by this technique and suggests that an optimal dose has been exceeded. From these data, they estimated 60 mg. of dihydrocodeine to be the analgesic equivalent of 10 mg. of morphine. The analgesia provided by 10 mg. of morphine could not be surpassed even by 90 mg. of dihydrocodeine. Since it has been possible to exceed the analgesia afforded by 10 mg. of morphine with all analgesics of the "morphine type" previously studied by this technique, it appears that dihydrocodeine is not a morphine-like analgesic but more nearly resembles codeine.

A similar study was performed by Wallenstein and his associates (12) in which dihydrocodeine was administered to patients with chronic pain accompanying cancer. They estimated that 68 mg. of dihydrocodeine was equivalent to 10 mg. of morphine. Seed *et al.* (13) in a subsequent report concurred in the estimate that the analgesic activity of 68 mg. of dihydrocodeine is equivalent to 10 mg. of morphine. However, on the basis of the peak of analgesic activity, they calculated 53 mg. of dihydrocodeine to be equivalent to 10 mg. of morphine (95% confidence limits of 29 and 169 mg.). Eddy *et al.* (14) reported that 30 mg. of dihydrocodeine had analgesic potency equal to 10 mg. of morphine or 60-120 mg. of codeine.

Several studies were conducted in an attempt to evaluate the effectiveness of dihydrocodeine in obstetrical patients. Ruch and Ruch (15) used dihydrocodeine in the first and second stages of labor in private obstetrical patients. In its analgesic potency, 30 mg. of dihydrocodeine appeared to be equivalent to 65-75 mg. of meperidine. Propert *et al.* (16), however, found that, at the doses used, meperidine was significantly more effective than dihydrocodeine. These results were obtained by the double-blind technique. Myers (17) studied the effect of dihydrocodeine in 50 obstetrical patients selected on the basis of presentation of a normal labor in which no complication was anticipated. Dihydrocodeine was given subcutaneously in a dose of

30 mg., regardless of the weight of the patient, when labor had progressed to about 5 cm. of cervical dilatation and the presenting part was at zero station. It was found that dihydrocodeine was more effective than a codeine-aspirin combination in alleviating postpartum uterine cramps. They concluded that dihydrocodeine is an effective, safe, and potent analgesic in labor.

Cass and Frederik (18) reported on the oral use of dihydrocodeine bitartrate in patients suffering from chronic diseases and having various degrees of discomfort, primarily in the moderately-severe to severe range. The results indicated 60 mg. to be more effective than 45 mg., and 45 mg. to be more effective than 30 mg. of dihydrocodeine. They also obtained an identical analgesic effect with 60 mg. of codeine and 60 mg. of dihydrocodeine. Keesling and Keats (19) also investigated the oral effectiveness of dihydrocodeine. The patients studied were those who had dental extractions under local anesthesia and who returned to the clinic with symptoms of alveolar osteitis, including moderate to severe pain. A double-blind experimental design was employed, the evaluations being made by two oral surgeons. Dihydrocodeine bitartrate (30 mg. orally) was found to be more effective than aspirin (600 mg.). However, the percentage of side-effects (sleepiness, dizziness, nausea, vomiting) was also considerably greater with dihydrocodeine. The authors point out the hazards of drawing conclusions from uncontrolled drug trials especially in out-patients and office patients, for 61% of the 67 patients who received a placebo obtained adequate relief of pain.

In an evaluation using normal subjects, Keasling and Gross (20) compared the effects of codeine, dihydrocodeine, aspirin, and a placebo on the radiant heat threshold using an adaptation of the Wolff-Hardy-Goodell technique. The doses employed were 10 and 20 mg. of codeine or dihydrocodeine and 300 mg. of aspirin; all were given orally in random sequence under double-blind conditions. None of the medications differed significantly in their effect from the placebo or from each other, a result which might have been expected considering the doses employed and the route of administration. Intravenous use of dihydrocodeine bitartrate as an adjunct to thiopentone-nitrous oxide anesthesia was found to provide satisfactory anesthesia without significant side-effects (21).

To summarize, dihydrocodeine has been reported to be an effective analgesic which does not quite attain the potency of morphine. It

is effective orally and parenterally in various types of pain—its optimal parenteral dose being 30 mg. The duration of action of dihydrocodeine is slightly less than that of morphine (8, 9, 13), although Wallenstein *et al.* (12) considers dihydrocodeine and morphine to have essentially the same duration of action when given in approximately equal analgesic doses.

Studies conducted with laboratory animals point to the same general relationship between dihydrocodeine, morphine, and codeine. Haffner (22), in 1929, reported on the analgesic properties of dihydrocodeine in mice. In 1934, Eddy (23) studied the analgesic activity of dihydrocodeine given intramuscularly to cats and found it to be more effective than codeine by the tail-pressure method. Based on data obtained by this method, Eddy and Reid (24) calculated the minimum effective dose of morphine, dihydrocodeine, and codeine to be 0.75, 7.20, and 8.04 mg./Kg. of alkaloidal base, respectively The minimum effective dose was defined as that amount of substance which caused, in at least 4 out of 5 animals, an increase in the pressure required to evoke a response when applied to the terminal portion of the cat's tail. Morphine exhibited a longer duration of action than codeine or dihydrocodeine. In 1955, Haas (25) investigated the activity in mice of these same three compounds against heat and electrical stimuli. He found no significant difference between the effectiveness of morphine and dihydrocodeine which were both approximately twice as effective as codeine.

Eddy *et al.* (14) reported on the analgesic activity and duration of action of morphine, dihydrocodeine, and codeine given subcutaneously in mice. In contrast to the results of Haas (25), these invesigators found a significant difference between morphine and dihydrocodeine. Their results may be summarized as follows:

	ED_{50}	
	Analgesia (*mg./Kg.*)	*Duration* (*minutes*)
Morphine	2.1	129
Dihydrocodeine	12.4	130
Codeine	14.2	67

Macht (26) also found the duration and intensity of action of dihydrocodeine to be greater than codeine when tested on guinea pigs by the induction coil method.

In order to determine the specificity of analgesic and antitussive activity of morphine, dihydrocodeine, and codeine, Friebel *et al.* (27) calculated the effective dose for abolition of the cough reflex in guinea pigs and the effective dose for analgesic activity. They found that these effects are not correlated; codeine and dihydrocodeine have a preferential effect against cough while morphine is more specific as an analgesic. Similar conclusions were also drawn by Mutch (28).

Antitussive Activity. Fraenkel, in 1913, (2) was the first to comment on the antitussive action of dihydrocodeine; he found it to be twice as effective as codeine. Dahl (29), in the same year, also found the dihydrogenated compound to be more effective against cough than codeine. A comparison of oral doses of 25 mg. of dihydrocodeine with 35-45 mg. of codeine indicated that the former was more effective and produced no greater incidence of side-effects than codeine. A more recent antitussive evaluation was performed by Haas (25). He evoked the cough reflex in cats by electrical stimulation of the laryngeal nerve and found that the dose required for 50% suppression of the reflex was 0.5 mg./Kg. for morphine, 2 mg./Kg. for dihydrocodeine, and 3 mg./Kg. for codeine. These results are reasonably well correlated with clinical reports (28).

Respiratory, Circulatory, and other Central Nervous System Effects. Since respiratory depression is so characteristic of the morphine-like analgesics and constitutes such an important disadvantage of this group of compounds, dihydrocodeine received considerable attention after the report by Gravenstein *et al.* (8) that the drug produced no greater respiratory depression in normal persons than a placebo. They determined the minute volume using room air or 5% carbon dioxide in 10 normal volunteers. Placebo, dihydrocodeine (30 mg.), and morphine (10 mg.), were shown to be increasingly depressant in the order listed. The difference between the respiratory depressant effect of dihydrocodeine and morphine was found to be significant, however, the difference between dihydrocodeine and placebo was not statistically significant. These relationships were similar under both conditions of respiratory measurement; i.e., room air and 5% carbon dioxide. Comparable results were obtained by Beecher (9). Eckenhoff, Helrich, and Rolph (30) administered higher doses to healthy young male subjects. Fifty or 60 mg. of dihydrocodeine were injected intramuscularly in all sub-

jects except one who received 75 mg. These investigations suggest that dihydrocodeine, in the doses used, has a slight respiratory depressant effect which is less, however, than that observed with a series of morphine-like analgesics. The respiratory response was less than that produced by intramuscular injection of 60 mg. of codeine sulfate. The depressant effect appeared less prominent if respiration was stimulated by increased carbon dioxide tension. In large doses, dihydrocodeine stimulates the central nervous system, occasionally causing convulsions. High levels of carbon dioxide might conceivably potentiate such a stimulant action.

The effects of dihydrocodeine and morphine on respiration were studied by Seed *et al.* (13, 31) by measuring the displacement of the alveolar ventilation—alveolar pCO_2 response curve. A double-blind, randomized-sequence, cross-over study was carried out in six subjects. Dihydrocodeine in doses of 30 and 60 mg. and morphine in doses of 5 and 10 mg. were given intramuscularly. From the displacement values, 77 mg. of dihydrocodeine was calculated as equivalent to 10 mg. of morphine in respiratory depressant activity. It appeared to these investigators that the effects of dihydrocodeine and morphine on the response curve are primarily due to an action on the respiratory control mechanism and not to changes in cerebral circulation, cerebral metabolism, airway resistance, or physiological dead space. They conclude that equal analgesic doses of dihydrocodeine and morphine produced equal degrees of respiratory depression.

Keats *et al.* (11) determined the respiratory effects of 30 and 60 mg. of dihydrocodeine and 10 mg. of morphine in 7 healthy subjects. Thirty mg. of dihydrocodeine slightly depressed respiration at one hour after drug administration, but respiration was restored to normal within three hours. Sixty mg. of dihydrocodeine more markedly depressed respiration, but this depression was significantly less than that produced by 10 mg. of morphine. The three hour post-treatment data suggested that dihydrocodeine was shorter acting than morphine at both dosage levels. In a subsequent study, Keats *et al.* (32) compared the effects of dihydrocodeine bitartrate and morphine on respiration in 30 normal subjects. Alveolar ventilation and end-tidal CO_2 tension were measured simultaneously before and after drug administration, both in room air and 3-4% CO_2 inhalation. At a dose of 30 mg., dihydrocodeine only slightly depressed respira-

tion at one hour following administration and, after three hours, the respiration was normal.

Levin (21) injected 100 mg. of dihydrocodeine intravenously into a patient under thiopentone anesthesia. Respiration was depressed to the point of apnea. Rapid recovery followed the administration of oxygen by intermittent compression of the rebreathing bag and other supplemental measures. Swerdlow (33), in a similar study, compared the respiratory changes produced by small intravenous doses of dihydrocodeine and pethidine in 20 patients under thiopentone anesthesia. Dihydrocodeine, 0.25 mg./Kg., was significantly less depressant than pethidine, 0.5 mg./Kg. The experiment was repeated with another 20 patients using twice the dose (0.5 mg./Kg.) of dihydrocodeine; again, respiratory depression was significantly less than in the pethidine group.

The respiratory effect of dihydrocodeine in obstetrical patients was studied by several investigators. Ruch and Ruch (15) found that administration of 30 mg. of dihydrocodeine in the first and second stages of labor produced very little respiratory depression in the newborn. Myers (17) reported that 30 mg. of dihydrocodeine was associated with 55% less over-all fetal respiratory depression than with 100 mg. of meperidine, as indicated by the time required to establish normal cry and respiration. Considering the level of analgesia obtained, dihydrocodeine was indicated as the safer drug. These workers believe, however, that dihydrocodeine is not devoid of respiratory depressant activity in the fetus.

Anticipating the possible usefulness of dihydrocodeine as an antitussive agent, Segal, Goldstein, and Attinger (34) evaluated its respiratory effect in patients with chronic broncho-pulmonary diseases. Respiratory depression, which is an inherent property of most compounds in the opiate group, is a serious deterrent to their use in these conditions. The three patients studied had chronic bronchitis and chronic pulmonary emphysema. In these disorders, respiratory depression from any cause may lead to serious complications in the form of alveolar hypoventilation, retention of CO_2, respiratory acidosis, and possibly death. The studies consisted of measurements of the minute ventilation, tidal volume, respiratory rate, and expired CO_2. With respiratory depression, a decrease in ventilation with an accompanying rise in expired CO_2 would be noted. The results showed no significant decrease in ventilation or rise in expired CO_2

which might be indicative of respiratory depression secondary to the intravenous administration of dihydrocodeine.

Wright (35), in 1934, studied the respiratory effects of morphine, codeine, and related substances in the rabbit. Dihydrocodeine bitartrate in doses of 30 mg./Kg. or more caused an increase in the reflex excitability of the rabbit which resulted in an increase in oxygen consumption. The respiratory rate before and during CO_2 administration was decreased by doses between 5 and 50 mg./Kg., but the effect on rate at the higher doses was partially compensated by the increased activity of the animal. The greatest decrease in minute volume occurred with 20 mg./Kg.; with larger doses, it reverted toward normal to an extent which roughly paralleled the hyperactivity of the animal. The tidal volume was increased in all doses greater than 10 mg./Kg.

Wright and Barbour (36) calculated the doses of morphine and dihydrocodeine which caused a 20% reduction in respiratory rate, minute volume, and CO_2 minute volume. The results obtained (doses expressed as mg./Kg.) were as follows:

Alkaloidal base	*Respiratory rate/minute*	*Minute volume*	*CO_2 minute volume*
Morphine	0.38	0.53	0.45
Dihydrocodeine	2.90	5.20	3.20

In a later study, Wright and Barbour (37) reported that four alkaloids derived from dihydrocodeine by substitutions in the 6-carbon position were all more potent respiratory depressants than the parent compound. Eddy (38), in 1936, reported on an investigation of the respiratory depressant effect of certain analgesics in rabbits. The minimal effective respiratory depressant doses were found to be as follows: morphine, 0.32; dihydrocodeine, 2.40; and codeine, 2.40 mg./Kg. (alkaloidal base). These data show good correlation with those of Wright and Barbour (36). Small *et al.* (39) presented similar results. The minimal dose required for a respiratory effect in rabbits was 0.15 mg./Kg. for morphine, 0.9 mg./Kg. for dihydrocodeine, and 1.3 mg./Kg. for codeine. The ratio of these doses approximates those reported by Eddy (38).

The effect of dihydrocodeine on circulation was investigated in some detail by Eckenhoff *et al.* (30). Blood pressure and heart

rate were measured in a group of healthy males by the use of an intra-arterial capacitance manometer. Ten of these individuals were subjected to a 50-60 degree head-up tilt for a period of fifteen minutes (unless severe hypotension or fainting occurred), after which time the subject was promptly returned to the horizontal position. Dihydrocodeine predisposed the subjects to hypotension as evidenced by this tilt test. The fact that 3 out of 7 subjects fainted following tilt would suggest that this drug is not very different from morphine in its effect upon the circulation. In a group of 8 subjects in the same age group, all of whom received 20 mg. of morphine, only 2 persons fainted following tilt.

In the experiments of Gravenstein *et al.* (8), 30 mg. of dihydrocodeine did not produce any significant change in blood pressure or pulse. This does not necessarily contradict the results of Eckenhoff (30) since the criteria for estimating the effect on circulation were different.

Myers (17) administered 30 mg. of dihydrocodeine subcutaneously to 50 patients in labor. No evidence of a cardiac depressant effect on the fetus *in utero* was noted on the basis of hourly records of fetal heart tones, a consideration of utmost importance if the drug is to be employed as an obstetrical analgesic.

Foster (40), in 1934, measured the effects of codeine and dihydrocodeine on the blood pressure of trained unanesthetized dogs with the aid of a specially constructed sphygmomanometer cuff attached to the foreleg. Codeine was found to have 3 times the depressor potency (systolic-diastolic) pressure of dihydrocodeine (free base), was about 3 times more potent in decreasing the pulse pressure, and 1½ times more potent in increasing the heart rate than dihydrocodeine. The author notes that the increase in heart rate was probably a compensatory reaction to the fall in blood pressure. The same investigator (41) also reported that morphine and codeine produced a decrease in blood pressure in anesthetized cats, while dihydrocodeine increased blood pressure initially in a dose of 0.6 mg./Kg. of base. Higher doses of dihydrocodeine, 2-5 mg./Kg., caused a decrease in blood pressure. These results again indicate that dihydrocodeine has about ⅓ the depressor potency of codeine.

Other central depressant effects were noted by Eddy and Ahrens (42) in a study of the central action of morphine, codeine, and dihydrocodeine in maze-trained rats. Codeine and dihydrocodeine

produced effects on the maze-trained rats qualitatively similar to those of morphine; however, the former were weaker in action. The M. E. D. for morphine was found to be 4.5 mg. (alkaloidal base); whereas, 16 mg. of codeine or 14.1 mg. of dihydrocodeine were required to produce equal degrees of depression. Eddy (38) also reported on the depressant action of morphine, codeine, and dihydrocodeine in rats on the basis of changes produced in the righting reflex. The M. E. D. for these three compounds were as follows: morphine 6.75, dihydrocodeine 14.19, and codeine 36.18 (mg./Kg. of base). These data also indicate dihydrocodeine to be between codeine and morphine in depressant activity. Macht (26) also showed that dihydrocodeine produced greater depression in albino rats than codeine.

The recent study of Keats *et al.* (11) on normal subjects lends evidence to the minor depressant effect of dihydrocodeine at low doses. They reported that the side-effects produced by 30 mg. of dihydrocodeine were only slightly greater than those following a placebo. The most frequently observed reaction to this dose was mild dizziness and a feeling of drunkenness. The subjective effects of 60 mg. were significantly greater than those of 30 mg. They approached the effects of morphine in both type and frequency, but remained significantly less frequent than morphine. The reactions to 60 mg. were more unpleasant than to 30 mg., with an increased incidence of a feeling of drunkenness, grogginess, psychic depression, and nausea. Dihydrocodeine, at both 30 and 60 mg. doses, differed from morphine chiefly in its lack of sedative effects and less frequent production of nausea and vomiting. Patients receiving dihydrocodeine did not sleep despite the presence of such effects as dizziness, grogginess, and the feeling of drunkenness. Other subjective reactions to 60 mg. of dihydrocodine, such as headache, difficulty in concentration, shaking, palpitations, nervousness, itching, impairment of accommodation, and dry mouth were significantly less than with morphine. This substantiated the report of Gravenstein (8) that morphine (10 mg.) elicited a greater number of side-effects than dihydrocodeine (30 mg.) or placebo. As previously noted, 30 mg. of dihydrocodeine produced no more side-effects than placebo. Dihydrocodeine or placebo did not produce a significant change in "dysphoria-euphoria"; whereas, morphine significantly increased dysphoria.

The minimal sedative activity of dihydrocodeine may offer some sphere of usefulness in treatment of the elderly since these people are exceptionally sensitive to the sedative action of the narcotics in current use (43).

Gastrointestinal Effects. Like other morphine-like alkaloids, dihydrocodeine has an emetic action if given in sufficient dosage; however, as an emetic, it is considerably weaker than morphine. Eddy (38) calculated the M. E. D. on intramuscular injection in cats to be 0.22 for morphine, 3.60 for dihydrocodeine, and 16.08 for codeine (mg./Kg. of base). Previously, Eddy and Reid (24) reported that 1 out of 5 animals vomited following administration of ⅓ of the analgesic dose of morphine. Dihydrocodeine and codeine produced only nausea and only with twice the analgesic dose or more.

In clinical trials, 30 mg. of dihydrocodeine produced no greater nausea and vomiting than a placebo (8, 10, 11, 32). Increasing the dose to 60 and 90 mg. resulted in some nausea, although even at these higher doses the incidence of gastrointestinal distress was still less than with 10 mg. of morphine (11).

The effect of morphine, dihydrocodeine, and codeine on intestinal motility in the rabbit was investigated by Eddy (23) in 1934. The M. E. D. (mg./Kg. of base, subcutaneously) which completely suppressed intestinal evacuation was 4.5 for morphine, 5.8 for dihydrocodeine, and 16.0 for codeine. Krueger and Gay (44), in 1933, studied the modifications of intestinal movements induced by dihydrocodeine and codeine in unanesthetized dogs with Thiry-Vella loops of the ileum. Four mg./Kg. of dihydrocodeine given subcutaneously increased intestinal tone in each of 5 dogs, while 2 mg./Kg. increased tone in 3 of 5 dogs. The M. E. D. was between 1 and 4 mg./Kg. Dihydrocodeine was more effective than codeine in enhancing intestinal tone; the M. E. D. for codeine ranged from 3 to more than 9 mg./Kg.

In 1958, Gray (45) performed similar investigations of the effects of morphine sulfate and dihydrocodeine bitartrate on unanesthetized Thiry-Vella dogs. Dihydrocodeine exhibited approximately one-thirtieth the intestinal spasmogenic potency of morphine. In *in vitro* studies using isolated rabbit and dog jejunum, dihydrocodeine stimulated the intestine of both species at lower concentrations than did morphine.

Addiction Liability. Dihydrocodeine is not devoid of addiction liability. Himmelsbach (46), in 1941, made a comprehensive study of the addiction characteristics of morphine, codeine, and dihydrocodeine. His method may be basically outlined as follows: (a) selection of addicts with active physical dependence, (b) preliminary stabilization of patients on morphine, (c) replacement of morphine with a substitute drug for at least one week, (d) withdrawal of the substitute drug. From such a procedure, it can be determined whether or not a drug will satisfy previously established physical dependence. The maintenance of physical dependence by a substitute drug is considered strong evidence that such drug is capable of producing addiction. The abstinence syndrome which appears following withdrawal of the substitute drug is thought to be the equivalent of that which would occur if addiction to the substitute drug were primary rather than secondary.

Potency values are obtained by comparing the mean amounts of single, equally effective, physical-dependence-satisfying doses of morphine and of the substitutes. To standardize the results, these values are corrected to be equivalent to 50 mg. of morphine sulfate. Values considered to express satisfactorily the duration of physical-dependence action are obtained by scoring the abstinence syndrome intensity (ASI) at hourly intervals following the last dose and using the time at which the group mean ASI has reached 50% of its maximum.

Application of these methods indicated that physical dependence was satisfied by dihydrocodeine. Several patients complained that it caused unpleasant dreams and itching. The abstinence syndrome which followed its withdrawal was definitely less severe than that of morphine. With morphine taken as a standard at 50 mg., the dose-equivalent for dihydrocodeine was calculated to be 175 mg., and the duration of the physical-dependence action was 20 hours as compared with 14 hours for morphine.

Acute Toxicity. In 1934, Eddy (23) reported on the acute toxicity of dihydrocodeine in mice and rabbits. Subcutaneous injections of dihydrocodeine in mice produced initial depression accompanied by moderate muscular weakness, usually erection of the tail, and occasionally turning movements. Later, reflex activity increased, but only moderately, and clonic convulsions occurred with 75% or more of the fatal dose. Often, there occurred trembling and irregular twitching of the muscles without the development of a generalized

convulsion. Dihydrocodeine in rabbits also produced initial depression and muscular weakness followed by increased reflex activity, increased muscle tone, twitching, and trembling, especially on stimulation. With 75% of the fatal dose, convulsions were manifested. The average fatal dose (AFD) of dihydrocodeine (alkaloidal base) was 225 mg./Kg. for mice and 129 mg./Kg. for rabbits. With dihydrocodeine, deeper and more persistent depression developed, reflexes were increased less, convulsions were less regular, less severe, and occurred only with a greater percentage of the fatal dose than with codeine. Toxicity was less than codeine in rabbits but approximately the same as codeine in mice.

In 1936, Eddy (38) reported values for acute toxicity and convulsant action with subcutaneous injections of morphine, dihydrocodeine, and codeine in white mice. These data may be summarized as follows:

	*Toxic Dose (A. F. D.)** *mg./Kg.*	*Convulsant Dose mg./Kg.*
Morphine	531	531
Dihydrocodeine	225	168
Codeine	241	161

* (A. F. D.) = average fatal dose; the amount of substance which kills more than 50% of the animals.

In 1939, the same investigator (47) conducted a study to determine whether or not the toxicity of these compounds varied with age in the rabbit. The average fatal dose, minimal convulsant dose, and incidence of convulsions were determined in rabbits ranging from 1 to 24 weeks of age. The curve of toxicity values (AFD) for dihydrocodeine corresponded closely in form to that of morphine, showing a similar initial rise, rapid at first, continuing more gradually from the fifth to the twelth week, and succeeded by a gradual decline to the twenty-fourth week. That a comparatively narrow range in individual susceptibility to dihydrocodeine existed was indicated by the small spread between the minimal fatal and the highest recovery doses. Dihydrocodeine was again found to be somewhat less convulsant than codeine but more convulsant than morphine.

More recently, Macht (26) reported the minimum lethal dose in mice to be 185 mg./Kg. for codeine and 180 mg./Kg. for dihydrocodeine. This agrees quite well with previously reported data.

Laboratory and clinical studies indicate that dihydrocodeine is considerably more effective than codeine but less effective than morphine in regard to analgesic and antitussive activity. The optimum analgesic dose of dihydrocodeine given subcutaneously in humans has been estimated to be 30 mg./70 Kg. of body weight. Increasing the dose to as much as 90 mg. in the average subject does not significantly improve the degree of analgesia obtained. With a dose of 30 mg., objective and subjective side reactions were minimal compared to 10 mg. of morphine, which constitutes an approximately equi-analgesic dose. Sufficiently large doses of dihydrocodeine have been found capable of eliciting all of the characteristic effects of the morphine-like analgesics; i.e., respiratory and circulatory depression, constipation, nausea and vomiting, etc. Dihydrocodeine is considered to be capable of producing addiction. Addiction liability lies between that of morphine and codeine, but probably closer to the latter. Dihydrocodeine appears to constitute a moderately effective analgesic, characterized by an unusually low incidence and severity of untoward reactions in relationship to its potency, with a rather versatile range of application in the relief of moderate-severe pain of various origins.

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CHEMOTHERAPEUTIC MANAGEMENT OF RETICULOSARCOMA

By John R. Sampey *

FIVE chemical agents account for four-fifths of the 285 cases of reticular-cell sarcomas treated in this study of chemotherapeutic agents since 1949, and these same chemicals induced 108 of the 125 responses described in the more than 100 published investigations. These same agents have also proved effective in the treatment of leukemias and lymphomas.[1] Table I summarizes the chemotherapeutic management of reticulosarcoma.

TABLE I

CHEMOTHERAPEUTIC MANAGEMENT OF RETICULOSARCOMA

Chemicals	*No. of Cases*	*No. of Remissions*		*No. of References*
		Good	*Fair*	
N-mustards	125	17	36	43
TEM	39	9	12	20
ACTH/Cortisone	31	2	12	19
Antibiotics	30	1	12	9
Colchicines	16	4	3	7
Miscellaneous	44	9	8	14

Nitrogen Mustards. N-mustards account for 40 per cent of the investigations and 45 per cent of the patients treated in this study. However, only 17 of the 53 regressions could be described as good, and a regression rate of less than 50 per cent calculated from reports which gave both the number of patients treated and the number responding leaves much to be desired. Mrazek reported serious bone marrow depression, especially when N-mustards followed irradiation. HN2, HN3, R48, CB1348, and nitromin have all been tested clinically in studies on reticulosarcoma.

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TEM. Triethylene melamine showed a higher remission rate than any other chemical in Table I (66 per cent when allowance was made for the 7 cases which were treated with TEM but without data given on their response). Mrazek also noted bone marrow depression with TEM.

ACTH/Cortisone. These hormones show only 2 good responses in 31 patients. Dubois-Ferriere described the promotion of septicemia by cortisone and antibiotics, and Taylor reported the death of a patient with reticulum cell sarcoma following withdrawal of large doses of prednisone.

Antibiotics. Of the investigators employing antibiotics for the management of reticulosarcoma, only Trounce showed any enthusiasm over the results. Actinomycin C has been the most frequently tested antibiotic for this neoplastic disease.

Colchicines. Deactylcolchicine and citostal have been the most used colchicines for reticulosarcoma. With 4 good and 3 fair regressions in 16 cases, these chemicals should be given further trials.

Miscellaneous Agents. The clinical trials with a dozen miscellaneous chemicals are too limited to have any statistical value, but they do point to several agents with interesting possibilities in reticulosarcoma therapy. Hyman described 5 subjective and 4 objective responses in 15 patients undergoing 6-MP treatment, and Seliger obtained some palliation with 6-MP and hydrocortisone, while Burchenal reported lymph node regression with this purine. Rosa recorded a good response in 2 of 3 patients on E39 therapy, but Olmer warned of hemorrhages in the use of this ethylene quinone. Winkler noted no palliation in phosphoramide therapy, but Wright obtained one complete and one partial regression with Thio-TEPA. Apffel reported good results in 2 patients treated with naphtho- and furanoquinones. Ariel administered mechlorethamine and oxytetracycline with good results. One reticulosarcoma responded some toward Consoli's use of sarcolysin, but DiPietro reported 2 reticulosarcomas were unaffected by phenylbutazone. Heilmeyer observed a fair response in one patient on myleran, an agent which has proved most effective in leukemia. Diamond found radiophosphorus ineffective in 9 cases of reticulosarcoma, but Romieu noted one of 3 patients had brief improvement with x-rays and P^{32} therapy. Spigliati noted no response

with a combination of aminopterin and citrovorum factor, and Wright found none in 2 cases of reticulosarcoma given guanazolo.

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ANTICONVULSANT ACTIVITY OF THREE NEW DIOXOLANE DERIVATIVES *

By Benjamin Weiss and Curtis G. T. Ewing

WITHIN the past few years, the ataractic or tranquilizing drugs have received enthusiastic reception by both the public and medical practitioners alike. A large number of compounds of diverse chemical structure and pharmacological activity are included in this general classification. Certain of these drugs, typified by meprobamate (Miltown or Equanil) and promoxolane (Dimethylane), also manifest skeletal muscle relaxant properties. They are therefore useful in the treatment of various anxiety and tension states associated with muscle spasm and abnormal motor activity.

In an attempt to develop compounds in this category with greater effectiveness and fewer side-effects, a series of new dioxolane derivatives were synthesized. On the basis of preliminary screening procedures, the following three compounds were selected from the new series for more extensive pharmacologic investigation: 2-methyl-2-pentyl-4-hydroxymethyl-1,3-dioxolane, carbamic acid ester (A-2653) [1]; 2-methyl-2-nonyl-4-hydroxymethyl-1,3-dioxolane, carbamic acid ester (A-2655) [1]; and 4-(o-toloxymethyl)-1,3-dioxolane (A-3020) [1].

Since it has been established that certain centrally-acting skeletal muscle relaxants manifest anticonvulsant properties (1-3), it was considered desirable to determine the presence or absence of such activity in these new dioxolanes. This report is primarily concerned with a study of various criteria of anticonvulsant activity of three dioxolane derivatives as compared with selected therapeutic agents in current clinical use.

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Experimental

Female Swiss Webster mice (Huntingdon Farm Strain), weighing from 18 to 22 Gm., maintained in temperature and humidity controlled quarters, were used throughout the experimental procedures. The mice were fasted for 12 hours before the test period but permitted continual free access to water. In all of the following procedures, the compounds investigated were administered in a suspension of 0.5% methylcellulose in distilled water.

Three dioxolane derivatives (compounds A-2653, A-2655, and A-3020) were compared with meprobamate (Miltown or Equanil) and trimethadione (Tridione) for their ability to reduce the convulsant and lethal effects of Metrazol and strychnine in mice. The dioxolanes were also compared with meprobamate and diphenylhydantoin (Dilantin) for their activity against electrically induced convulsions.

The maximal Metrazol seizure (M. M. S.) test, which measures the ability of a drug to afford complete protection against seizures induced by a standard dose of Metrazol, was conducted basically as outlined by Swinyard *et al.* (4). Various doses of the anticonvulsants under study were injected intraperitoneally—and in other studies administered orally—to groups of 20 mice. During each test period, at least one group of control animals received an intraperitoneal injection of the 0.5% methylcellulose suspension. After a 30 minute interval, 85 mg./Kg. of Metrazol (in distilled water) was administered subcutaneously to each test and control animal. The appearance of even a single threshold convulsion during a 2 hour period of constant observation was considered a positive response. Mortality occurring within 24 hours after injection of Metrazol was also recorded.

A similar procedure was followed in determining the protective activity of these compounds against the convulsive and lethal effects of 2.5 mg./Kg. of strychnine sulfate (in distilled water) injected intraperitoneally.

The maximal electroshock seizure (M. E. S.) test in mice measures the ability of a drug to abolish the hindlimb extensor component of the maximal seizure pattern induced by 50 milliamperes of current delivered for 0.2 second (4). Current was conducted from an Electroshock Seizure Apparatus [2] by corneal electrodes placed on the eye-

[2] Model 2-C, Hans Technical Associates, Palo Alto, California.

balls (previously moistened with a drop of 1% Butacaine Sulfate solution) of the mice. Stimulation was applied 30 minutes after administration of the anticonvulsants to the test animals and methylcellulose alone to the control groups.

The effect of compound A-2655, meprobamate, and methylcellulose suspension on the duration of hypnosis induced by intraperi-

TABLE I

ANTICONVULSANT ACTIVITY OF THREE DIOXOLANE DERIVATIVES COMPARED WITH MEPROBAMATE AND TRIMETHADIONE

Protection Against Convulsant and Lethal Effects of Metrazol [3]

Compound	*Dose mg./Kg. i.p.*	*N*	*Percent Protection Against Convulsant Effect of Metrazol*	*Percent Protection Against Lethal Effect of Metrazol*
Methylcellulose	—	100	3	36
Meprobamate	25	20	20	75
	50	20	40	90
	100	20	75	100
Trimethadione	100	20	20	60
	200	20	50	60
	400	20	100	100
A-2655	50	20	30	65
	100	20	50	90
	200	20	90	100
	400	20	100	100
A-2653	50	20	15	55
	100	20	20	60
	200	20	50	80
A-3020	50	20	10	40
	100	20	0	10
	200	20	0	15

[3] 85 mg./Kg. of Metrazol, subcutaneously, 30 minutes after injection of the test compound.

toneal injection of 100 mg./Kg. of hexobarbital sodium was also determined in mice. Varying doses of compound A-2655 and meprobamate were injected intraperitoneally 30 minutes before administration of the barbiturate. The interval between injection of hexobarbital and reappearance of the "righting reflex" (animal turns spontaneously over into normal position but continues to sleep) was recorded as the "sleeping time".

TABLE II

ANTICONVULSANT ACTIVITY OF THREE DIOXOLANE DERIVATIVES COMPARED WITH MEPROBAMATE AND TRIMETHADIONE

Protection Against Convulsant and Lethal Effect of Strychnine [4]

Compound	*Dose mg./Kg. i.p.*	*N*	*Percent Protection Against Convulsant Effect of Strychnine*	*Percent Protection Against Lethal Effect of Strychnine*
Methylcellulose	—	40	0	0
Meprobamate	100	10	0	0
	200	10	0	20
	400	10	0	30
Trimethadione	100	10	0	0
	200	10	0	0
	400	10	0	0
A-2655	100	10	0	30
	200	10	0	40
	400	10	10	90
A-2653	100	10	0	0
	200	10	0	0
	400	10	0	0
A-3020	100	10	0	0
	200	10	0	10
	400	10	0	10

[4] 2.5 mg./Kg. of strychnine sulfate, intraperitoneally, 30 minutes after injection of the test compound.

Results and Discussion

Reduction of the convulsant and lethal effects of Metrazol (85 mg./Kg.) in mice was obtained with various intraperitoneal doses of meprobamate, tridione, and dioxolane compound A-2653 and A-2655; whereas, compound A-3020 provided no protection against Metrazol toxicity (Table I). Of the compounds examined, meprobamate was most effective. A dose of 100 mg./Kg. of meprobamate administered intraperitoneally 30 minutes prior to the subcutaneous injection of Metrazol prevented the appearance of convulsions in 75 per cent of the animals, and protected all animals from death due

TABLE III

ANTICONVULSANT ACTIVITY OF THREE DIOXOLANE DERIVATIVES COMPARED WITH MEPROBAMATE AND DIPHENYLHYDANTOIN

Protection Against Maximal Electroshock Seizures[5]

Compound	*Dose mg./Kg. i.p.*	*N*	*Percent Protection Against Maximal Electroshock Seizures*
Methylcellulose	—	50	0
Meprobamate	100	20	10
	150	10	100
	200	10	100
Diphenylhydantoin	10	10	80
	20	10	100
A-2655	50	10	0
	75	10	90
	100	10	90
	200	10	100
A-2653	100	10	10
	200	10	80
	400	10	100
A-3020	50	10	10
	100	10	70
	200	10	70
	400	10	90

[5] MES, 50 mA for 0.2 second, administered via eyeball electrodes, 30 minutes after injection of the test compound.

to the convulsant. This dose produced only very mild tranquilization of the experimental animals. Doses of compound A-2655, which elicited comparable degrees of Metrazol antagonism, produced moderate sedation and mild ataxia. It is interesting to note that, in the groups which received compound A-3020 prior to Metrazol, the incidence of convulsions was not reduced and the number of deaths was increased in comparison to the control (methylcellulose-treated) group.

Oral administration of meprobamate and compound A-2655 in doses of 400, 500, and 600 mg./Kg. provided moderate protection against the convulsive and lethal effects of Metrazol in mice for as long as 4 hours. At all dose levels, meprobamate was considerably more active than the dioxolane compound. The degree of sedation observed with meprobamate was noticeably greater than that elicited by comparable oral doses of compound A-2655, which may indicate that the dioxolane is less readily absorbed than meprobamate.

In the dosages selected, none of the compounds examined inhibited convulsions elicited by 2.5 mg./Kg. of strychnine sulfate in mice (Table II). Meprobamate and compound A-2655 markedly

TABLE IV

PROLONGATION OF HEXOBARBITAL SODIUM "SLEEPING TIME" IN MICE BY MEPROBAMATE AND COMPOUND A-2655

Compound	*Dose mg./Kg. i.p.*	*N*	*Sleeping Time Minutes*	*Ratio*
Methylcellulose	—	40	33	1.0
Meprobamate	25	10	33	1.0
	50	20	39	1.2
	100	20	85	2.5
	200	9	175	5.3
A-2655	25	10	31	1.0
	50	20	40	1.2
	100	20	84	2.5
	200	6	153	4.6

All mice received Hexobarbital Sodium, 100 mg./Kg., intraperitoneally, 30 minutes after injection of the test compound.

reduced mortality only with doses that resulted in severe depression and flaccid paralysis.

Meprobamate, diphenylhydantoin, and the three dioxolanes provided significant protection against maximal electroshock seizures in mice (Table III). In contrast to the inhibition of chemically-induced convulsions, compound A-2655 appeared more active than meprobamate against electrically-induced seizures. The dioxolane A-2655 markedly reduced the effects of maximal electroshock in doses which produced no perceptible sedation or locomotor impairment.

Meprobamate was previously reported by Berger (1) to prolong the duration of hypnosis induced by hexobarbital sodium in mice. In this study, compound A-2655 and meprobamate were found to be approximately equipotent in regard to the prolongation of hexobarbital sodium "sleeping time" (Table IV).

Summary

1. Three dioxolane compounds (A-2653; A-2655; A-3020), selected as the most promising of a large series of new dioxolane derivatives, were compared with meprobamate and trimethadione in regard to their ability to reduce the convulsant and lethal effects of Metrazol and strychnine in mice. The most effective of the new dioxolanes, compound A-2655, was determined to be somewhat less active than meprobamate by both intraperitoneal and oral routes of administration.

2. Compound A-2655 provided greater protection against maximal electroshock seizures in mice than comparable doses of meprobamate. Diphenylhydantoin sodium, one of the most potent anticonvulsants, was considerably more effective than the dioxolane or meprobamate.

3. Compound A-2655 and meprobamate were approximately equally effective in prolonging hypnosis induced by hexobarbital sodium in mice.

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1959 MEETING OF THE PLANT SCIENCE SEMINAR

Frank L. Mercer, Secretary-Treasurer

The University of Illinois College of Pharmacy was host to the 36th. Annual Plant Science Seminar from August 7th. through the 10th. The Local Committee included the following:

Frank A. Crane, *Chairman* Ralph F. Voigt
Stanislaus J. Smolenski George L. Webster

Women's Activities—

Verle M. Crane Ethel V. Voigt
Anna Bee Webster

The Seminarians were welcomed by Dr. George L. Webster, Dean of the College of Pharmacy at the University of Illinois.

a. The Plant Science Seminar activities included a field trip to the University of Illinois Drug and Horticultural Experiment Station and to the Chicago Museum of Natural History. Papers dealing with research and teaching in pharmacognosy were presented at The Teachers Seminar in Pharmacognosy which was held August 9th. through the 13th. at the University of Illinois College of Pharmacy.

b. The Edwin Leigh Newcomb awards were presented by Dr. Heber W. Youngken, Sr. at the annual banquet. The undergraduate award was given to Mr. Robert E. Brummett of Oregon State College of Pharmacy, the graduate award to Dr. Ikram Hassan of the Philadelphia College of Pharmacy and Science, and the Teacher-researcher award to Dr. Virginia L. Bailey of Wayne State University College of Pharmacy.

The banquet address was given by Mohammed Samir Amer who spoke on "The Practice of Pharmacy in Egypt."

By unanimous approval of members at the business meeting of the Plant Science Seminar, a Constitution and By-Laws was adopted forming an organization to be known as The American Society of Pharmacognosy.

This Society has been formed by the pharmacognosists of the United States to formalize and perpetuate the standards and ideals of the Plant Science Seminar and has for its purpose ". . . to promote the growth and development of pharmacognosy, to provide the opportunity for association among the workers in that science and in related sciences, to provide opportunities for presentations of research achievements and to promote the publication of meritorious research." Membership is also open to graduate students and workers of other nations.

The following officers of the Seminar are to serve as officers of The American Society of Pharmacognosy until the first election of the Society:

Chairman .....Edson F. Woodward
First Vice-Chairman .....Mary L. Anderson
Second Vice-Chairman .....Frank J. Pokorny
Secretary-Treasurer .....Frank L. Mercer

Executive Committee:

J. Hampton Hoch Frank L. Mercer
Carl Johnson Arthur Schwarting
Edson Woodward

SELECTED ABSTRACTS

A Suppository of Hydrocortisone Hemisuccinate. Trillwood, W. *Pharm. J. 182*:357 (1959). Hydrocortisone hemisuccinate sodium, a freely water-soluble compound has been used in the form of a rectal drip for the treatment of ulcerative colitis. However, the solution is relatively unstable in aqueous solution and must be prepared only a short time before it is to be used. Prednisolone 21-phosphate has been found to be about equal in effectiveness with hydrocortisone hemisuccinate sodium and is more stable in aqueous solution.

The rectal drip administration of steroid compounds has been found to be an effective means of providing widespread coverage of the colon with the steroid being administered. However, it is a wasteful use of expensive compounds where the ulcerative area is confined to the lower portion of the colon. Consequently, suppositories have been tried in these conditions. They are also much more convenient for the patient to use.

In studies undertaken with a water-soluble dye (brilliant green), it was found that a cocoa butter base suppository provided greater spreadability over the mucous membranes of the colon than did a water-miscible suppository base, although the latter was miscible with the secretions of the colon. Clinically, there was little difference between the two bases as to their effectiveness.

The following formula for hydrocortisone hemisuccinate sodium suppositories was recommended by the author:

Hydrocortisone hemisuccinate sodium, fine powder	10 mg.
Cocoa Butter	1 Gm.

Since the steroid is insoluble in the cocoa butter, the author emphasized the importance of insuring even distribution throughout the base. Distribution should not be accomplished by the addition of a small amount of water because of the fact that the compound is unstable in aqueous solution.

A Comparison of the Effects of Hydrochlorothiazide With Chlorothiazide. Fleming, P. R., Zilva, J., Bayliss, R. I. S., and Pirkis, J. *The Lancet* No. 7085:1218 (1959). A comparison of the effectiveness of hydrochlorothiazide with chlorothiazide on convalescent patients, healthy patients, and edematous patients was reported. Hydrochlorothiazide was found to be clearly more potent weight for weight than chlorothiazide. In convalescent and healthy patients, the sodium excretion was about 20 times greater with the hydro derivative on a weight basis. The water excretion in convalescent patients showed about the same relationship but there was no significant difference in healthy patients. In edematous patients, there was considerable variation from patient to patient but usually the hydrochlorothiazide was about 10 times more potent than the parent compound. Thus, about one tenth as much hydrochlorothiazide as chlorothiazide would need to be administered to an edematous patient to obtain the same effect. The authors stated that a daily dose of 50 to 150 mg. of hydrochlorothiazide would appear to be required to obtain a satisfactory response in edematous patients.

Qualitative differences in the diuretic effect of the two compounds indicated that hydrochlorothiazide did not cause as much excretion of bicarbonate as did chlorothiazide; however, both drugs promoted the excretion of potassium to a similar and appreciable extent. Therefore, if treatment with either compound must be continued for several days, it is necessary to administer supplements of potassium chloride. Intermittent therapy is preferred for either compound.

The authors suggested that the greater potency of hydrochlorothiazide might be related to better intestinal absorption; to the fact that, unlike chlorothiazide, hydrochlorothiazide is not excreted in the bile and thus more is available for renal elimination; or to greater secretion of the drug by the renal tubules where it exerts its effect.

The Hydrolysis of Sodium Lauryl Sulfate. Read, R. R., and Fredell, W. G. *Drug and Cosm. Ind. 84*:178 (1959). Sodium lauryl sulfate is thought to be subject to hydrolysis in solution but little or no evidence has been reported as to the conditions under which hydrolysis occurs. The authors reported a study in which solutions of sodium lauryl sulfate were prepared, adjusted to various pH levels

between 1.1 and 10, and then subjected to storage temperatures of room, 37° C., and 50° C. The solutions were not buffered. When sodium lauryl sulfate undergoes hydrolysis, lauryl alcohol and sodium acid sulfate are formed. The change in titratable acidity was used as a measure of the amount of hydrolysis.

A solution of 14.5 per cent concentration adjusted to a pH of 1.1 was found to hydrolyze in water. At room temperature, about 225 days were required for 40 per cent hydrolysis to occur; at 70° C., about 120 hours for 70 per cent hydrolysis; and, at 100° C., about 80 minutes for 70 per cent hydrolysis. Thus, it is evident that the temperature has a pronounced effect on the rate of hydrolysis.

Using a normal range of storage temperatures of room, 37° C., and 50° C., a 5 per cent solution showed after 30 days storage approximately 2 per cent hydrolysis at room temperature; 5 per cent, at 37° C.; and 45 per cent, at 50° C. A 10 per cent solution showed under identical conditions about 2 per cent hydrolysis at room temperature; 8 per cent, at 37° C.; and 85 per cent, at 50° C. Therefore, the concentration also has an effect on the rate of hydrolysis.

In a comparison of the effects of pH on the degree of hydrolysis after one month storage at room, 37° C., and 50° C., it was found that solutions at a pH of 4 or above showed practically no hydrolysis. It appeared that a pH of less than 2.5 was needed to appreciably accelerate hydrolysis.

The authors concluded that solutions of sodium lauryl sulfate are inherently stable at their normal neutral pH. High temperatures and low pH are required to appreciably accelerate hydrolysis.

BOOK REVIEWS

Scoville's The Art of Compounding, Ninth Edition. Glenn L. Jenkins, Don E. Francke, Edward A. Brecht, and Glen J. Sperandio. 551 pp. The Blakiston Division, McGraw-Hill Book Company, Inc., New York, N. Y., 1957. Price: $11.00.

The ninth revision of this excellent textbook introduces much new material. It is similar to the eighth edition (1951) in style and format. The authors maintained two prime objectives: to present the principles underlying each subject and to illustrate and indicate the practical utility of these principles at the prescription counter. Several chapters have been expanded, and a new chapter on ophthalmic solutions has been added. The chapters on incompatibilities have been thoroughly revised.

The Art of Compounding is an expression of the ultimate work which underlies the proper approach to the mastery of dispensing. Professional competence in this field can be achieved only by drawing on the basic knowledge obtained in such courses as chemistry, pharmacology, physics, and biology. The usefulness of this textbook is not limited to students; it is also a valuable aid for the practicing pharmacist. It should be in the library of every professional person who practices the art of pharmacy.

ELSA EHRENSTEIN

Organic Syntheses, Vol. 38. John C. Sheehan, Editor. vii + 120 pp. John Wiley and Sons, Inc., 440 Fourth Ave., New York 16, New York, 1958. Price: $4.00.

This latest edition of the well-known series consists of 31 tested preparations covering many areas of organic chemistry. A new innovation is the presentation of infrared data for one of the compounds (monovinylacetylene). The subject index is cumulative for volumes 30-38. Three warning insertion sheets are included for ethyl azodicarboxylate, methoxyacetylene, and o-toluamide, the syntheses of which appeared in previous volumes. No laboratory or scientific library worthy of the name can afford to be without this informative series.

A. R. GENNARO

Medicinal Chemistry, Volume IV. By Wilbur S. Doran; edited by F .F. Blicke and R. H. Cox. ix + 334 pp. John Wiley and Sons, Inc., New York City, New York, 1959. Price: $12.00.

Dr. Doran has attempted to cover in this book the entire field of Barbituric Acid Hypnotics from its inception through 1956. This compendium, containing over 1200 references, lists almost 10,000 derivatives of barbituric acid. Where the information is known, pertinent pharmacologic data is presented.

The first portion is devoted to the history, chemistry, and pharmacology of the barbiturates. The latter and most extensive section of the book tabulates all known derivatives according to structure. An adequate formula and subject index round out this complete reference work.

This book is such a complete review of the barbiturate field that it should be in every chemical or pharmaceutical library.

A. R. GENNARO

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